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# Health and Environmental Effects Profile for 4,4'-Methylenebis(N,N-Dimethyl)Aniline

(U.S.) Environmental Protection Agency
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16. ABSTRACT

The Health and Environmental Effects Profile for 4,4'-methylenebis-(N,N-dimethyl)-aniline was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. 4,4'-Methylenebis-(N,N-dimethyl)aniline has been evaluated as a carcinogen. The human carcinogen potency factor ($q_1^*$) for 4,4'-methylenebis-(N,N-dimethyl)aniline is $1.15 \times 10^{-1}$ $(mg/kg/day)^{-1}$ for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for 4,4'-methylenebis-(N,N-dimethyl)aniline is 1000.

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# HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR 4,4'-METHYLENEBIS(N,N-DIMETHYL)ANILINE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
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## PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of $q_1^*$ (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

TABLE OF CONTENTS


| | | Page |
|---|---|---|
| 1. | INTRODUCTION | 1 |
| 1.1. | STRUCTURE AND CAS NUMBER | 1 |
| 1.2. | PHYSICAL AND CHEMICAL PROPERTIES | 1 |
| 1.3. | PRODUCTION DATA | 2 |
| 1.4. | USE DATA | 3 |
| 2. | ENVIRONMENTAL FATE AND TRANSPORT PROCESSES | 4 |
| 2.1. | AIR | 4 |
| 2.2. | WATER | 4 |
| 2.3. | SOIL | 4 |
| 3. | EXPOSURE | 5 |
| 4. | PHARMACOKINETCS | 7 |
| 4.1. | ABSORPTION | 7 |
| 4.2. | DISTRIBUTION | 7 |
| 4.3. | METABOLISM | 7 |
| 4.4. | EXCRETION | 11 |
| 5. | EFFECTS | 12 |
| 5.1. | CARCINOGENICITY | 12 |
| 5.2. | MUTAGENICITY | 17 |
| 5.3. | TERATOGENICITY | 21 |
| 5.4. | OTHER REPRODUCTIVE EFFECTS | 21 |
| 5.5. | CHRONIC TOXICITY | 21 |
| 5.6. | OTHER RELEVANT INFORMATION | 25 |
| 6. | AQUATIC TOXICITY | 27 |
| 7. | EXISTING GUIDELINES AND STANDARDS | 28 |
| 7.1. | HUMAN | 28 |
| 7.2. | AQUATIC | 28 |
| 8. | RISK ASSESSMENT | 29 |
| 9. | REPORTABLE QUANTITIES | 39 |
| 9.1. | REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY | 39 |
| 9.2. | WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY | 39 |
| 10. | REFERENCES | 47 |
| APPENDIX: | LITERATURE SEARCHED | 54 |

## LIST OF TABLES


| No. | Title | Page |
|---|---|---|
| 4-1 | Tissue Distribution of 4,4'-[$^{14}$C]-Methylenebis-(N,N-dimethylaniline) | 8 |
| 4-2 | Relative Mobilities of 4,4'-[$^{14}$C]-Methylenebis-(N,N-dimethylaniline) and Synthesized Metabolites | 10 |
| 5-1 | Oral Exposure to 4,4'-Methylenebis(N,N-dimethylaniline) | 13 |
| 5-2 | Mutagenicity Testing of 4,4'-Methylenebis(N,N-dimethylaniline) | 18 |
| 5-3 | Rat Subchronic Study Results | 22 |
| 5-4 | Mouse Subchronic Study Results | 24 |
| 5-5 | Acute Toxicity of 4,4'-Methylenebis(N,N-dimethylaniline) | 26 |
| 8-1 | Cancer Data Sheet for Derivation of $q_1^*$ | 31 |
| 8-2 | Cancer Data Sheet for Derivation of $q_1^*$ | 32 |
| 8-3 | Cancer Data Sheet for Derivation of $q_1^*$ | 33 |
| 8-4 | Cancer Data Sheet for Derivation of $q_1^*$ | 34 |
| 8-5 | Cancer Data Sheet for Derivation of $q_1^*$ | 35 |
| 8-6 | Cancer Data Sheet for Derivation of $q_1^*$ | 36 |
| 8-7 | Summary Data Sheet for Derivation of $q_1^*$ for 4,4'-Methylenebis(N,N-dimethylaniline) | 37 |
| 9-1 | Oral Toxicity Summary for 4,4'-Methylenebis(N,N-dimethylaniline) | 40 |
| 9-2 | Composite Scores for Toxicity of 4,4'-Methylenebis-(N,N-dimethylaniline) Administered to Rats and Mice in the Diet | 41 |
| 9-3 | 4,4'-Methylenebis(N,N-dimethylaniline) Minimum: Effective Dose (MED) and Reportable Quantity (RQ) | 42 |
| 9-4 | Oral Exposure to 4,4'-Methylenebis(N,N-dimethylaniline) | 43 |
| 9-5 | Derivation of Potency Factor (F) Agent: 4,4'-Methylenebis(N,N-dimethylaniline) | 46 |

## LIST OF ABBREVIATIONS

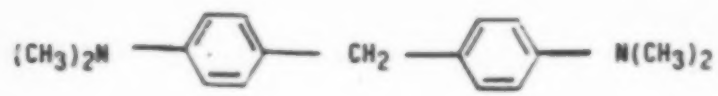
| | |
|---|---|
| ADI | Acceptable daily intake |
| bw | Body weight |
| CAS | Chemical Abstracts Service |
| CS | Composite score |
| GI | Gastrointestinal |
| i.p. | Intraperitoneal |
| $LD_{50}$ | Concentration lethal to 50% of recipients |
| MED | Minimum effective dose |
| MTD | Maximum tolerated dose |
| NADPH | Nicotinamide adenine dinucleotide phosphate |
| ppm | Parts per million |
| RLV | Rauscher leukemia virus |
| RQ | Reportable quantity |
| $RV_d$ | Dose-rating value |
| $RV_e$ | Effect-rating value |
| SCE | Sister-chromatid exchange |
| $TD_{LO}$ | Lowest-tolerated dose |
| TLC | Thin-layer chromatography |
| UDS | Unscheduled DNA synthesis |

# 1. INTRODUCTION

## 1.1. STRUCTURE AND CAS REGISTRY NUMBER

4,4'-Methylenebis(N,N-dimethylaniline) is known by several synonyms, including p,p'-methylenebis(N,N-dimethylaniline), tetramethyldiaminodiphenylmethane, p,p'-tetramethyldiaminodiphenylmethane, 4,4'-tetramethyldiaminodiphenylmethane, p,p'-dimethylaminodiphenylmethane, p,p'-bis(N,N-dimethylaminophenyl)methane, bis(p-dimethylaminophenyl)methane, bis(4-dimethylaminophenyl)methane, Michler's base, tetra-base, MDBA, methane base, Michler's Hydride and Michler's Methane. Current CAS usage is 4,4'methylenebis (N,N-dimethyl)benzenamine.

The structure and empirical formula for 4,4'-methylenebis(N,N-dimethylaniline) are as follows:




The empirical formula for 4,4'-methylenebis(N,N-dimethylaniline) is $C_{17}H_{22}N_2$ and the molecular weight is 254. The CAS Registry number for this compound is 101-61-1.

## 1.2. PHYSICAL AND CHEMICAL PROPERTIES

This compound occurs as yellowish leaflets or glistening, lustrous plates. Selected physical properties are listed below (Hawley, 1981; Windholz, 1976; Weast, 1972, unless otherwise stated):

| | |
|---|---|
| Melting point: | 90-91°C |
| Boiling point: | 390°C (sublimes without decomposition) |

| | |
|---|---|
| Vapor pressure: | 0.1 mm Hg at 148.9°C [vapor pressure of Ortholeum 304 (99% 4,4'-methylene-bis(N,N-dimethylaniline), which was manufactured by Du Pont de Nemours and marketed until November 15, 1978 (E.I. Du Pont de Nemours and Co., 1981]. |
| Solubility in water | insoluble |
| Solubility in other solvents: | very soluble in diethylether, benzene and carbon disulphide; soluble in acetone, acids, hot ethanol; slightly soluble in cold ethanol |

## 1.3. PRODUCTION DATA

4,4'-Methylenebis(N,N-dimethylaniline) can be produced from dimethylaniline by 1) heating it with 40% formaldehyde and concentrated hydrochloric acid, 2) reacting it with diacetyperoxide or 3) reacting it with tert-butyl-perbenzoate (Windholz, 1976).

Total verifiable United States production of this chemical in 1977 was reported to be between 0.1 and 1.0 million pounds (U.S. EPA, 1985). This amount was produced totally by the Hilton-Davis Chemical Company, Cincinnati, OH. However, E.I. Du Pont de Nemours and Company was also listed as a producer; American Cyanamid Company was listed as an importer and possible producer; and BASF Wyandotte Corporation was listed as an importer only, but no volume information was given. The USITC (1978) reported a production figure of 998,000 pounds for 1977. This was down markedly from the reported 1974 production figure of 1.862 million pounds (USITC, 1976).

SRI (1984) lists two manufacturers of this compound: American Cyanamid, Marrietta, OH, and Sterling Drug, Inc., Hilton-Davis Chemical Company Division, Cincinnati, OH. The USITC (1984) reports that 8800 pounds of this chemical were imported in 1983.

## 1.4. USE DATA

4,4'-Methylenebis(N,N'dimethylaniline) is believed to be used primarily as a dye intermediate (IARC, 1982; Bannister and Elliot, 1978). The Color Index lists six dyes and one pigment that can be made from it (The Society of Dyers and Colourists, 1971). In 1979, only one of the dyes, basic yellow 2, was listed as being produced in the United States (USITC, 1980). The hydrochloride of 4,4'-methylenebis(N,N-dimethylaniline) has been reported to be useful as a reagent for lead (Windholz, 1976).

The NIOSH (1981) Tradename Ingredient Index lists two products that contain this compound: Metalcoat 2 lithium grease, which contains 1% of this compound, and Du Pont Ortholeum 304 antioxidant, which contains 99% of this compound and was last made and marketed in 1978 (E.I. Du Pont de Nemours and Co., 1969). Ortholeum 304 has been used in very small quantities (0.1-1%) in oils and greases.

## 2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

### 2.1. AIR

Pertinent data regarding the environmental fate and transport processes in the atmosphere involving 4,4'-methylenebis(N,N-dimethyl)aniline were not located in the available literature as cited in the Appendix.

### 2.2. WATER

Experimental data regarding the fate and transport of 4,4'-methylenebis(N,N-dimethylaniline) in the aquatic environment were not located in the available literature as cited in the Appendix. The insolubility of the compound in water suggests that bioaccumulation in aquatic organisms is likely and may be significant in waters containing 4,4'-methylenebis(N,N-dimethylaniline). Also, adsorption to particulate organic matter and sediment in water is possible due to its water insolubility; data from Nelson and Hites (1980), discussed in Chapter 3, would seem to confirm this possibility.

### 2.3. SOIL

Experimental data regarding the environmental fate and transport processes of this compound in soil were not located in the available literature as cited in the Appendix. The insolubility of the compound in water suggests that leaching in soil is unlikely to be significant. Also, the molecular structure-activity relationships of the compound predict a soil adsorption coefficient >5000 (Sabljic, 1984), which relates to immobility in soil. The compound is soluble in acids (Hawley, 1981; Weast, 1972); therefore, leaching by acidic water may have some importance, but experimental monitoring data are not available.

## 3. EXPOSURE

Nelson and Hites (1980) reported the presence of aromatic amines in and near the Buffalo River. Both sediment and soil samples were tested. 4,4'-Methylenebis(N,N-dimethylaniline) was found in all the sediment samples tested in concentrations ranging from 0.1-0.2 ppm. The compound was also found in one of the two soil samples tested at a level of 20 ppm; it was not detected in the second soil sample. These levels were not corrected for extraction efficiencies and, thus, represent minimum values. Since the Buffalo River is dredged annually, the sediment levels reflect only the accumulation of the compound during the 7- to 8-month period between the previous dredging and the collection of the sediment samples. The authors suggested that the site where the soil samples were taken may have been used as a chemical dump by a dyestuff manufacturing plant located near the sampling sites. This conclusion was based on the high concentrations and close structural similarity of the various aromatic amines present in the soil samples. These amines were intermediates in the synthesis of two dyes manufactured at this dye plant, crystal violet and malachite green, among others. Evidence for the orignal presence of intermediates involved in these syntheses was also found. Furthermore, the authors suggested that these compounds may have been leached from the soil and accumulated in the sediments, as demonstrated by the close proximity of the soil sampling sites to the river and the similarity in structure and concentration ratios of several of the aromatic amines present in both the soil and sediment samples. The U.S. EPA STORET Data Base contains no observations for 4,4'-methylenebis(N,N-dimethylaniline).

Facilities manufacturing 4,4'-methylenebis(N,N-dimethylaniline) may release the compound to the atmosphere through air vent emissions as dust

(U.S. EPA, 1981); however, no monitoring data are available to confirm its presence in the atmosphere in the vicinity of production plants or anywhere else.

Dermal exposure is possible in the use of products formulated with small amounts of this compound (see Section 1.4.). Also, consumers exposed to materials with dyes that have this compound as an intermediate (or by-product) may be exposed to any unreacted compound through skin contact (NCI, 1979). These dyes include C.I. Basic Yellow 2, C.I. Basic Orange 14, C.I. Solvent Yellow 34, C.I. Solvent Orange 15, methylene red and crystal violet. Another possible source of exposure would be the consumption of fish caught in the Buffalo River, especially bottom-feeders; however, no data regarding the bioconcentration of this compound or its presence in these fish were located to confirm this suggestion.

## 4. PHARMACOKINETICS

### 4.1. ABSORPTION

McCarthy et al. (1982) administered 60 mg of 4,4'-[$^{14}$C]-methylene-bis(N,N-dimethylaniline) by gavage to a single male Osborne-Mendel rat (336 g). Of the administered radioactivity, 15.2% was detected in the urine collected over 24 hours, and 73% was detected in the homogenized carcass; however, the percentage remaining in the GI tract was not determined. Therefore, it is not possible to estimate the extent to which the chemical was absorbed by the GI tract.

### 4.2. DISTRIBUTION

The tissue distribution of 4,4'-[$^{14}$C]-methylenebis(N,N-dimethyl-aniline) (1.5 mg, 16 µCi in 1 mℓ of propylene glycol) was evaluated following i.p. injection of the dose into each of 15 male Osborne-Mendel rats weighing 320-349 g (McCarthy et al., 1982). Five rats were sacrificed at 1, 3 and 24 hours after injection, and individual tissues were removed and stored at -80° for later analysis. Results of the tissue distribution experiment are summarized in Table 4-1. At 1 and 3 hours, the highest concentrations of radioactivity were in the small intestine, fat and liver, and at 24 hours, in the large intestine and fat. At 24 hours, rats retained 40% of the i.p. dose. The slow clearance of 4,4'-methylenebis(N,N-dimethyl-aniline) may be related to its accumulation in fatty tissue, since the methylene group contributes to the lipophilic nature of the compound.

### 4.3. METABOLISM

<u>In vitro</u> metabolism of 4,4'-[$^{14}$C]-methylenebis(N,N-dimethylaniline) was studied in liver microsomes prepared from male Osborne-Mendel rats pretreated with phenobarbital (McCarthy et al., 1982). Metabolites were identified by TLC, comparing their relative mobilities with synthetic

TABLE 4-1

Tissue Distribution of
4,4'-[$^{14}$C]-Methylenebis(N,N-dimethylaniline)[a]

| Organ or Tissue | Radioactivity (pCi/mg tissue) | | |
|---|---|---|---|
| | 1 Hour | 3 Hours | 24 Hours |
| Serum | 8.5±1.2[b] | 18.5±0.58 | 18.1±1.7 |
| Liver | 91.9±17.2 | 75.4±3.8 | 42.5±5.5 |
| Spleen | 26.4±5.8 | 18.3±3.1 | 9.3±2.4 |
| Kidney | 38.0±3.5 | 37.5±4.2 | 19.2±1.7 |
| Fat | 184.4±101 | 250.9±154.5 | 133.2±6.0 |
| Stomach | 130.3±60.8 | 35.1±4.9 | 16.7±8.1 |
| Large intestine | 30.6±4.3 | 31.9±5.3 | 140.0±30.4 |
| Small intestine | 219.3±18.8 | 209.0±22.9 | 96.8±18.7 |
| Other | 191.6[c] | 215.5[c] | 108.8[c] |
| Recovery (%)[d] | 84.0 | 75.6 | 38.1 |

[a]Source: McCarthy et al., 1982

[b]Mean ± S.E.

[c]Standard error not determined

[d]Represents percentage of recovery of total administered dose, including counts in remaining organs and carcass

standards. Results are presented in Table 4-2. Demethylation, acetylation and hydroxylation of 4,4'-methylenebis(N,N-dimethylaniline) were the major metabolic transformations occurring in rats. The major microsomal metabolite was the unsymmetrical didemethylated derivative (N,N-dimethyl-4,4'-methylenedianiline), accounting for 44.7% of the total radiolabel present (Table 4-2). Unchanged 4,4'-methylenebis(N,N-dimethylaniline) accounted for 29.3% of the radiolabel, and by the tridemethylated derivative accounted for 11.8% of the total radiolabel (Table 4-2). The tetrademethylated derivative of the test compound accounted for 6.9% of the radiolabel. The results are indicative of a selective order by which the demethylation enzymes remove methyl groups from the molecule.

Metabolites of 4,4'-methylenebis(N,N-dimethylaniline) were isolated and identified in the urine of two male Osborne-Mendel rats (236 and 245 g) given a *per os* dose of 200 mg/kg (30 µCi/animal). A 24-hour urine sample was collected and the metabolites were extracted and identified by TLC, which revealed that 43% of the dose excreted in the urine was unmetabolized 4,4'-methylenebis(N,N-dimethylaniline), 36% was N,N'-diacetyl-4,4'(hydroxymethylene)dianiline and 21% was an unidentified compound (McCarthy et al., 1982). *In vivo*, the demethylated derivative of 4,4'-methylenebis(N,N-dimethylaniline) underwent further metabolism to the N,N'-diacetylated-hydroxylated methylene derivative excreted in the urine. No hydroxylated products were identified in the *in vitro* microsomal mixture. McCarthy et al. (1982) suggested several explanations: the liver enzymes may not have been adequately induced by phenobarbital; the liver may not be the site for hydroxylation; the *in vitro* conditions were not similar to *in vivo* metabolism; or the compounds used were not substrates for the hydroxylating enzymes.

TABLE 4-2

Relative Mobilities of 4,4'-[$^{14}$C]-Methylenebis(N,N-dimethylaniline) and Synthesized Metabolites[a]

| Compound | $R_f$ [b] | Total cpm from 40-Minute Microsomal Mixture[c] (%) |
|---|---|---|
| 4,4'-Methylenebis(N,N-dimethyl aniline) | 0.83 | 29.3 |
| N,N-Dimethyl-4,4'methylene-dianiline | 0.77 | 5.3 |
| N,N-Dimethyl-4,4'-methylene-dianiline | 0.72 | 44.7 |
| N-Methyl-4,4'-methylene-dianiline | 0.65 | 11.8 |
| 4,4'-Methylenedianiline | 0.54 | 6.9 |
| Total | | 98.0 |

[a]Source: McCarthy et al., 1982

[b]Relative mobilities of compounds on TLC (Silicaca Gel GF, 250 µm) in chloroform:acetone (2:1). The retention time was 14-1 minute

[c]Relative amount of each metabolite recovered from the chloroform extract of a 40-minute incubation mixture of 4,4'methylenebis(N,N-dimethylaniline), NADPH and rat liver 9000 x g supernatants

## 4.4. EXCRETION

The disposition of 4,4'-methylenebis(N,N'dimethylaniline) was determined in one male Osborne-Mendel rat (366 g) given a 60 mg dose of 4,4'-[$^{14}$C]-methylenebis(N,N-dimethylaniline) (15.8 μCi) by stomach tube (McCarthy et al., 1982). Urine, feces and $CO_2$ were collected for 24 hours. At 24 hours, the rat was sacrificed and homogenized. After 24 hours, 73% of the per os dose was retained by the animal, 15.2% of the dose was excreted in the urine and 5.1% in the feces. No detectable radioactivity was excreted as expired $CO_2$.

## 5. EFFECTS

### 5.1. CARCINOGENICITY

The National Cancer Institute conducted a 2-year bioassay of 4,4'-methylbis(N,N-dimethylaniline) in rats and mice for possible carcinogenicity (NCI, 1979; Murthy, 1980; Weisburger, 1983; Weisburger et al., 1984; IARC, 1982; U.S. EPA, 1981). All animals were inspected twice daily. Body weights were recorded once a week for the first 6 weeks, every two weeks for the next 12 weeks and at monthly intervals thereafter. Necropsies were performed on all animals found dead or when the study was terminated (91 weeks for mice and 104 weeks for rats). Gross and microscopic examinations were performed on all major tissues, organs and gross lesions. Tissues were prepared by standard histologic techniques. The Fisher Exact test was used to compare tumor incidence of a control group with that of a treated group at each dose level (0.05 level of significance), and the Cochran-Armitage test for linear trend was used to determine if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance.

Groups of 50 male and 50 female F344 rats were given 375 and 750 ppm in the diet for 59 weeks followed by a 45-week observation period (NCI, 1979). Twenty animals of each sex served as controls. Subchronic studies were performed at several oral dosages on groups of five animals of each sex. The dose level was selected on the basis of survival, a 20% decrease in body weight gain and the observation of rough hair and arched backs in treated animals. Survival after 104 weeks was comparable among groups (74-88%) and sufficient numbers were at risk for late-developing tumors.

In rats, the incidence of neoplasms considered to be compound-related are presented in Table 5-1. In male rats, the incidence of follicular-cell carcinoma of the thyroid was associated positively with dose ($p<0.001$,

TABLE 5-1

Oral Exposure to 4,4-Methylenebis(N,N-dimethylaniline)[a]

| Species/ Strain | Sex | Dose[b] (ppm) | Duration of Treatment (weeks) | Duration of Study (weeks) | Purity of Compound | Vehicle or Physical State | Target Organ | Tumor Type | Tumor Incidence (P value) |
|---|---|---|---|---|---|---|---|---|---|
| rats/F344 | M | 0<br>375<br>750 | 59 | 104 | technical grade | diet | thyroid | follicular-cell carcinoma | 1/18 (p<0.001))[b]<br>4/50<br>21/46 (p=0.002)[c] |
| | | 0<br>375<br>750 | | | | | | follicular-cell adenoma | 0/18<br>0/50<br>13/46 |
| | | 0<br>375<br>750 | | | | | | follicular-cell carcinoma/adenoma | 1/18 (p<0.001)[b]<br>4/50<br>34/46 (p<0.001)[c] |
| | | 0<br>375<br>750 | | | | | | C-cell carcinoma/adenoma | 2/18<br>2/50<br>4/46 |
| rats/F344 | F | 0<br>375<br>750 | 59 | 104 | technical grade | diet | thyroid | follicular-cell carcinoma | 0/20 (p<0.001)[b]<br>3/46<br>23/45 (p<0.001)[c] |
| | | 0<br>375<br>750 | | | | | | follicular-cell adenoma | 0/20<br>1/46<br>13/45 |
| | | 0<br>375<br>750 | | | | | | follicular-cell carcinoma/adenoma | 0/20 (p<0.001)[b]<br>4/46<br>36/45 (p<0.001)[c] |
| | | 0<br>375<br>750 | | | | | | C-cell carcinoma/adenoma | 2/20<br>2/46<br>1/45 |
| mice/ B6C3F1 | M | 0<br>1250<br>2500 | 78 | 91 | technical grade | diet | liver | hepatocellular carcinoma | 3/20<br>9/50<br>6/48 |
| | | 0<br>1250<br>2500 | | | | | | hepatocellular carcinoma/or adenoma | 5/20 (p=0.025)[b]<br>12/50<br>22/48 |



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TABLE 5-1 (cont.)

| Species/ Strain | Sex | Dose[b] (ppm) | Duration of Treatment (weeks) | Duration of Study (weeks) | Purity of Compound | Vehicle or Physical State | Target Organ | Tumor Type | Tumor Incidence (P value) |
|---|---|---|---|---|---|---|---|---|---|
| mice/ B6C3F1 | F | 0<br>1250<br>2500 | 78 | 91 | technical grade | diet | liver | hepatocellular carcinoma | 0/19<br>1/49<br>1/48 |
| | | 0<br>1250<br>2500 | | | | | | hepatocellular carcinoma/or adenoma | 1/19 ($p=0.002^b$)<br>19/49 ($p=0.005^c$)<br>23/48 ($p=0.001^c$) |

QUALITY OF EVIDENCE

Stengths of Study: Several dose levels studied in both sexes of more than one species. A sufficient number of animals per species and sex was evaluated (50). Control groups consisted of 20 animals/sex/species. Comprehensive histologic examination was performed. Appropriate statistical methods were employed.

Overall Adequacy: Adequate

[a]NCI, 1979

[b]Cochran-Armitage test for linear trend, probability level for significance $p<0.05$

[c]One tailed Fisher Exact test for comparison of tumor indicence between treated group and control group, probability level for significance $p<0.05$

Cochran-Armitage). The incidences were 1/19 control males, 4/50 low dose males and 21/46 high-dose males. The Fisher Exact comparison between control and high dose males was also significant ($p=0.002$). A significant ($p<0.001$) dose-response was also obtained when the incidences of follicular-cell carcinomas and adenomas were combined (1/18 control males, 4/50 low-dose males and 34/46 high-dose males); however, the departure from linear trend was significant. The Fisher Exact comparison between high-dose and control was significant ($p<0.001$).

Similar results were observed in female rats. The Cochran-Armitage test indicated a significant ($p<0.001$) positive association between dose and the incidence of follicular-cell carcinoma of the thyroid and the combined incidences of follicular-cell carcinoma/adenoma of the thyroid ($p<0.001$). These were supported by significant ($p<0.001$) Fisher Exact tests comparing the high-dose group with the control group. In female rats only, a positive association was obtained between dose and incidence of neoplastic nodules of the liver ($p=0.036$); however, the relationship between the high-dose group and controls was not significant. The incidences were 0/20 control females, 0/49 low-dose females and 4/47 high-dose females. The incidences of thyroid C-cell carcinomas or adenomas were not significantly different compared with control in treated male or female rats.

Based on pathological and statistical results, 4,4'-methylenebis(N,N-dimethylaniline) was carcinogenic to male and female F344 rats, inducing follicular-cell neoplasms of the thyroid gland under conditions of the bioassay.

Groups of 50 male and 50 female B6C3F1 mice were given 1250 and 2500 ppm in the diet for 78 weeks, followed by a 13-week observation period (NCI, 1979). Twenty animals of each sex served as controls. Subchronic studies

were performed at several oral dosages on groups of five animals of each sex. A decrease in the rate of body weight gain in dosed mice was the major criteria on which the dose level was selected for the chronic study, as no animals died in the subchronic study. Survival for all groups in the chronic study was 84-100%.

In mice, neoplasms considered to be compound-related are presented in Table 5-1. In male mice, a significant (p=0.025) positive association between dose and the combined incidence of hepatocellular carcinoma/adenomas was observed; however, none of the pair-wise comparisons was significant. No other statistical tests were significant for tumor incidence in male mice at any site. The combined incidences of hepatocellular carcinoma/adenoma in male mice were 5/20 controls, 12/50 low-dose and 22/48 high-dose males.

A positive association (p=0.002) between dose and the combined incidence of hepatocellular carcinoma/adenoma was also observed in female mice. Significant comparisons between high-dose and control (p=0.001) and low-dose and control (p=0.005) were observed. No other statistical tests were significant for tumor incidence in female mice at any other site. The combined incidences of hepatocellular carcinoma/adenoma in female mice were 1/19, controls; 19/49, low-dose; and 23/48, high-dose females.

Results of the bioassay indicate that the administration of 4,4'-methylenebis(N,N-dimethylaniline) was carcinogenic to female B6C3F1 mice, inducing a combination of hepatocellular carcinomas or hepatocellular adenomas under the conditions of the study.

Negative results were obtained with 4,4'-methylenebis(N,N-dimethylaniline) in the strain A mouse pulmonary tumor induction bioassay (Maronpot et al., 1983). In this bioassay, 20, 25, 50 and 100% of the MTD was given

by 1.p. injection 3 times/week for 8 weeks to groups of 20 or 30 mice. The mice were killed 16 weeks after the last injection and grossly visible pulmonary tumors were counted.

## 5.2. MUTAGENICITY

Results of mutagenicity testing of 4,4'-methylenebis(N,N-dimethylaniline) are reported in Table 5-2. Equivocal results were obtained in bacterial tests. The compound was found to be nonmutagenic in several strains of Salmonella typhimurium in the presence of liver microsomes from Aroclor-induced or uninduced rats by Simmon (1979a), Rosenkranz and Poirier (1979), Scribner et al. (1980) and Leifer et al. (1981), but was found to be mutagenic in S. typhimurium strains TA98 and TA100 in the presence of hepatic microsomes from rats or mice by Dunkel and Simmon (1980), Waalkins et al. (1981), McCarthy et al. (1982, 1983). Microsomal metabolites of 4,4'-methylenebis(N,N-dimethylaniline) gave positive results in S. typhimurium strain TA100 in the presence of S-9 (McCarthy et al., 1982).

4,4'-Methylenebis (N,N-dimethyl)aniline gave positive results in mice in the host-mediated assay in which S. typhimurium strain TA1538 was the genetic indicator and the chemical was administered intramuscularly at 125 mg/kg. Negative results were obtained in the same assay using strain TA1530 as the genetic indicator. Oral administration of 1600 mg/kg of the chemical gave negative results when Saccharomyces cerevisiae D3 was used as the genetic indicator (Simmon et al., 1979).

A dosage of 50 µg/mL 4,4'-methylenebis(N,N-dimethylaniline) to rabbit lymphocytes resulted in a slight increase in the number of SCE/metaphase when tested in the absence of liver microsomes from rats (Waalkens et al., 1981). The compound did not induce mitotic recombination in S. cerevisiae D3 when tested in the presence or absence of Aroclor-induced rat liver microsomes (Simmon, 1979b).

TABLE 5-2

Mutagenicity Testing of 4,4'Methylenebis(N,N-dimethylaniline)

| Assay | Indicator/ Organism | Compound and/or Purity | Application | Concentration or Dose | Activating System | Response | Comment | Reference |
|---|---|---|---|---|---|---|---|---|
| Reverse mutation | Salmonella typhimurium TA98, TA100, TA1535, TA1536, TA1537, TA1538 | technical grade | plate incorporation | 250 µg or 0.95 µmol/plate | ±S-9 | - | Negative in all strains | Simmon, 1979a |
| Reverse mutation | S. typhimurium TA1535, TA1538 | technical grade | plate incorporation | 250 µg/plate | ±S-9 | - | Negative in both strains | Rosenkranz and Poirier, 1979; Leifer et al., 1981; |
| Reverse mutation | S. typhimurium TA98 TA100 TA1535 TA1537 TA1538 | 99% pure | plate incorporation | 25-100 µg/plate | ±S-9 | ± - - - - | NC | Waalkens et al., 1981 |
| Reverse mutation | S. typhimurium TA100 | NR | plate incorporation | 0-250 µg/plate | ±S-9 | ± | Mutagenic in the presence of S-9; response linear from 1-33 µg/plate | McCarthy et al., 1983 |
| Reverse mutation | S. typhimurium | NR | plate incorporation | NR | ±S-9 | ± | Mutagenic response only with metabolic activation | Dunkel and Simmon, 1980 |
| Reverse mutation | S. typhimurium TA100 | unmetabolized 4,4'-methylene-bis(N,N-di-methyl)aniline; microsomal metabolites; major urinary metabolites | plate incorporation | 0-1000 µg/plate | ±S-9 | ± | Neither the unmetabolized compound, the major urinary metabolite nor the demethylated intermediates of microsomal metabolism were direct-acting mutagens; however, all of the microsomal metabolites tested and the unmetabolized compound were mutagenic in the presence of S-9. | McCarthy et al., 1982 |



0699p

08/20/85

TABLE 5-2 (cont.)

| Assay | Indicator/ Organism | Compound and/or Purity | Application | Concentration or Dose | Activating System | Response | Comment | Reference |
|---|---|---|---|---|---|---|---|---|
| Reverse mutation | S. typhimurium | technical grade | plate incorporation | 4-400 µg/plate | ±S-9 | - | NC | Scribner et al., 1980 |
| | TA1530 | | | | | - | | |
| | TA1535 | | | | | - | | |
| | TA1538 | | | | | + | | |
| | Saccharomyces cerevisiae D3 | | | | | - | | |
| Differential toxicity | Escherichia coli pol A⁻, pol A⁺ | technical grade | liquid suspension | 20 µg/mL | none | + | NC | Rosenkranz and Poirier, 1979 Leifer et al., 1981 |
| Reverse mutation (host-mediated) | S. typhimurium | technical grade | Adult Swiss-Webster mice in vivo | 2-5500 mg/kg | NA | | NC | Simmon et al., 1979; Legator et al., 1982 |
| | TA1530 | | | | | - | | |
| | TA1535 | | | | | - | | |
| | TA1538 | | | | | + | | |
| | Saccharomyces cerevisiae D3 | | | | | - | | |
| Mitotic recombination | S. cerevisiae D3 | technical grade | cell suspension | 1% w/v | ±S-9 | - | NC | Simmon, 1979b |
| SCE | rabbit lymphocytes | 99% purity | cell culture | 0-250 µg/mL | ±S-9 | + | At 50 µg/mL, an increase ($p<0.01$) in the number of SCEs/metaphase in the absence of S-9; no increase in SCEs/metaphase in the presence of S-9 | Waalkens et al., 1981 |
| DNA damage | mouse lymphoma L5178Y | NR | cell culture | NR | none | + | Compound was positive in all four mammalian cell assays. | NTP, 1983; Mitchell et al., 1982 |
| | RLV infected rat hepatocytes | | | | | + | | |
| UDS | rat hepatocytes | NR | cell culture | NR | none | + | NC | Mitchell et al., 1982 |
| Transformation | BALB/c 3T3 | NR | cell culture | NR | none | + | NC | Mitchell et al., 1982 |

TABLE 5-2 (cont.)

| Assay | Indicator/ Organism | Compound and/or Purity | Application | Concentration or Dose | Activating System | Response | Comment | Reference |
|---|---|---|---|---|---|---|---|---|
| UDS | rat hepatocytes | NR | cell culture | $10^{-2}$ mg/mℓ, $5x10^{-3}$ mg/mℓ, $5x10^{-4}$ mg/mℓ | NA | + | A toxic effect was obtained at $10^{-2}$mg/mℓ; a weak induction of DNA repair occurred at the other two doses. | Williams et al., 1982 |
| Cell transformation | Syrian Golden hamster embryo cells | NR | cell culture | 0.1-100 µg/mℓ | ±S-9 | +<br>+ | The compound transformed hamster embryo cells in the absence of exogenous activation at doses of 1 and 10 µg/mℓ. | Pienta and Kawalek, 1981 |

NA = Not applicable

NC = No comment

NR = not reported



0699p

08/20/85

At doses of 1 and 10 μg/mℓ, 4,4'-methylenebis(N,N'-dimethylaniline) induced morphological transformation of hamster embryo cells (Pienta and Kawalek, 1981) in the absence of exogenous activation. In addition, the compound gave positive results in mammalian cell systems for the detection of mutagenesis, DNA damage and repair and cell transformation (Mitchell et al., 1982; Anonymous, 1983; Williams et al., 1982).

## 5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of 4,4'-methylenebis(N,N-dimethylaniline) were not located in the available literature cited in the Appendix.

## 5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects of 4,4'methylenebis(N,N-dimethylaniline) were not located in the available literature cited in the Appendix.

## 5.5. CHRONIC AND SUBCHRONIC TOXICITY

Before the initiation of the 2-year NCI (1979) bioassay of 4,4'methylenebis(N,N-dimethylaniline), subchronic toxicity tests were con- ducted with both rats and mice. Groups of five male and five female F344 rats were given the test compound in the diet at 0, 145, 315, 680, 1466 and 3155 ppm for 4 weeks, followed by a 2-week observation period (NCI, 1979). At the end of the test period, all animals were necropsied. Results of the subchronic study in rats are reported in Table 5-3. Mean body weight gain relative to controls, survival and incidence of rough hair and arched backs are shown in Table 5-3. No other compound-related abnormalities were observed. The con- centrations selected for the chronic bioassay were 375 and 750 ppm.

Groups of five male and five female B6C3F1 mice were given the test compound in the diet at concentrations of 370, 500, 810, 1180, 1740, 3750,

TABLE 5-3

Rat Subchronic Study Results[a]

| ppm | Mean Body Weight Gain (%)[b] | | Survival[c] | | Observation of Rough[c] Hair and Arched Backs | |
|---|---|---|---|---|---|---|
| | Males | Females | Males | Females | Males | Females |
| 3155 | -135 | -61 | 5/5 | 5/5 | 5/5 | 0/5 |
| 1466 | -107 | -49 | 5/5 | 5/5 | 0/5 | 0/5 |
| 680 | -37 | -11 | 5/5 | 5/5 | 0/5 | 0/5 |
| 315 | -13 | -1 | 5/5 | 5/5 | 0/5 | 0/5 |
| 145 | -26 | +6 | 5/5 | 5/5 | 0/5 | 0/5 |
| 0 | NA | NA | 5/5 | 5/5 | 0/5 | 0/5 |

[a]Source: NCI, 1979

[b]+ is indicative of mean body weight gain greater than that of controls;
- is indicative of mean body weight gain less than that of controls.

[c]Number of animals observed/number of animals originally in group.

NA = Not applicable

5500, 8080 and 11,830 ppm for 4 weeks followed by a 2-week observation period (NCI, 1979). Five male and five female mice served as controls. At the end of the test period, all animals were necropsied. Results of the the subchronic study in mice are summarized in Table 5-4, which also lists mean body weight gain relative to controls and survival at the end of the test period. No other compound-related abnrmalities were observed. The dosages selected for the 2-year chronic bioassay were 1250 and 2500 ppm.

In the chronic study, male rats receiving the high dose (750 ppm) exhibited slight mean body weight depression compared with controls after week 30. A dose-related trend (not significant) in mean body weight depression was apparent in female rats after week 35 (NCI, 1979). The Tarone test for association between dosage and mortality was not significant for male or female rats. In male rats, 44/50 (88%) of the high dose, 39/50 (78%) of the low dose and 16/20 (80%) of the controls survived for at least 104 weeks. In female rats, 37/50 (74%) of the high dose, 41/50 (82%) of the low dose and 17/20 (85%) of the controls survived on test for 104 weeks. No other clinical signs were observed. Nonneoplastic lesions observed in dosed but not control rats were associated with the thyroid gland. Dosed animals had increased incidences of follicular cysts, hyperplasia and C-cell hyperplasia. The incidence of follicular cell cysts in rats were: 0/20, control males; 4/50, low-dose males; 3/46, high-dose males; 0/20, control females; 3/46, low-dose females; 1/45, high-dose males. Incidences of follicular hyperplasia were 0/20, control males; 0/50, low-dose males; 7/46, high-dose males; 0/20, control females; 1/46, low-dose females; 5/45, high-dose females. Incidences of C-cell hyperplasia were 0/20, control males; 5/50,

TABLE 5-4

Mouse Subchronic Study Results[a]

| ppm | Mean Body Weight Gain (%)[b] | | Survival[c] | |
|---|---|---|---|---|
| | Males | Females | Males | Females |
| 11,830 | -2 | -1 | 5/5 | 5/5 |
| 8,080 | +3 | -2 | 5/5 | 5/5 |
| 5,500 | -12 | -5 | 5/5 | 5/5 |
| 3,750 | -4 | -4 | 5/5 | 5/5 |
| 1,740 | -2 | -10 | 5/5 | 5/5 |
| 1,180 | -4 | -8 | 5/5 | 5/5 |
| 810 | 1 | +2 | 5/5 | 5/5 |
| 550 | +6 | -8 | 5/5 | 5/5 |
| 370 | +3 | -4 | 5/5 | 5/5 |
| 0 | NA | NA | 10/10 | 10/10 |

[a]Source: NCI, 1979

[b]+ is indicative of mean body weight gain greater than that of controls;
- is indicative of mean body weight gain less than that of controls.

[c]Number of animals observed/number of animals originally in group.

NA = Not applicable

low-dose males; 1/46, high-dose males; 0/20 control females; 1/46, low-dose females; 1/45, high-dose females. No other compound-related nonneoplastic lesions were observed.

After week 30, the mean body weights of dosed male mice were lower than controls (NCI, 1979). A dose-related trend in decreased body weight of female mice was observed after week 30. The Tarone test for association between dosage and mortality was not significant for male or female mice. In male mice, 50/50 (100%) of the high-dose, 47/50 (94%) of the low-dose and 20/20 (100%) of the controls survived for at least 91 weeks. In female mice, 42/50 (84%) of the high-dose, 46/50 (92%) of the low-dose and 18/20 (90%) of the controls survived for at least 91 weeks. Compound-related non-neoplastic poliferative lesions induced in mice were found in the thyroid gland. The incidences of thyroid papillary hyperplasia in mice were 0/18, control males; 10/45 (22%), low-dose males; 13/49 (27%), high-dose males; 0/16, control females; 7/43 (16%), low-dose females; 6/43 (14%), high-dose females. Incidences of adenomatous goiter were 0/18, control males; 4/45 (9%), low-dose males; 22/49 (45%), high-dose males; 0/16, control females; 25/43 (58%), low-dose females; 35/43 (81%), high-dose females. Two high-dose males were diagnosed as having colloid goiter, a stage of adenomatous goiter, which would make the total goiter incidence 24/49 (49%) for this group. Other inflammatory and degenerative lesions observed in both control and treated groups occur commonly in aging B6C3F1 mice and were not compound-related.

## 5.6. OTHER RELEVANT INFORMATION

Acute toxicity studies in animals are summarized in Table 5-5.

TABLE 5-5

Acute Toxicity of 4,4'-Methylenebis(N,N-dimethylaniline)

| Species | Parameter | Route | Dose | Reference |
|---|---|---|---|---|
| Rat | $LD_{50}$ | NR | $\geq$500 mg/kg | Dieke et al., 1947 |
| Rat | $LD_{Lo}$ | oral | 500 mg/kg | NIOSH, 1979 |
| Rat | $TD_{Lo}$ | oral | 8500 mg/kg | NIOSH, 1979 |
| Mouse | $LD_{50}$ | oral | 3160 mg/kg | NIOSH, 1979 |
| Mouse | $TD_{Lo}$ | oral | 82 g/kg | NIOSH, 1979 |
| Mouse | TD | oral | 164 g/kg | NIOSH, 1979 |

*Source: U.S. EPA, 1981

NR = Not reported

## 6. AQUATIC TOXICITY

Data regarding the toxic responses and residual concentration of 4,4'-methylenebis(N,N-dimethylaniline) in aquatic organisms were not located in the available literature as cited in the Appendix.

## 7. EXISTING GUIDELINES AND STANDARDS

### 7.1. HUMAN

Pertinent guidelines and standards, including U.S. EPA ambient water and air quality criteria, drinking water standards, FAO/WHO ADIs, U.S. EPA or FDA tolerances for raw agricultural commodities or foods, and ACGIH, NIOSH or OSHA occupational exposure limits were not located in the available literature as cited in the Appendix.

### 7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of 4,4'-methylene bis(N,N-dimethylaniline) were not located in the available literature as cited in the Appendix.

## 8. RISK ASSESSMENT

Dietary administration of 4,4'-methylenebis(N,N-dimethylaniline) to F344 rats for 2 years at concentrations of 8, 375 and 750 ppm resulted in an increased incidence of follicular-cell neoplasms of the thyroid gland in male and female F344 rats. Administration of the compound to B6C3F1 mice at dosages of 0, 1250 and 2500 ppm in the diet for 91 weeks resulted in an increased combined incidence of hepatocellular carcinomas or adenomas in female mice. The incidences of these tumors are presented in Table 5-1.

Results of mutagenicity testing of 4,4'-methylenebis(N,N-dimethylaniline) in bacterial systems are equivocal (see Table 5-3). Positive results were obtained in S. typhimurium TA98 and TA100 in the presence of hepatic microsomes from rats or mice by Dunkel and Simmon (1980), Waalkins et al. (1981) and McCarthy et al. (1982, 1983) but negative responses were found in TA98, TA100 and other strains of S. typhimurium in the presence of liver microsomes from Aroclor-induced or uninduced rats (Simmon, 1979a; Rosenkranz and Poirier, 1979; Leifer et al., 1981; Scribner et al., 1980). Positive results were obtained in the host-mediated assay in mice when S. typhimurium strain TA1538 was the genetic indicator and negative results were obtained when S. cerevisiae D3 was the genetic indicator. The compound gave positive results in several mammalian cell assays for the detection of mutagenesis, DNA damage, and cell transformation (Mitchell et al., 1982; Pienta and Kawalek, 1981; NTP, 1983; Williams et al., 1982). Information regarding teratogenic and reproductive effects were not located in the available literature as cited in the Appendix.

Dosages for the 2-year NCI (1979) bioassay in rats and mice were determined in a subchronic study (see Table 5-3). A decrease in mean body weight gain relative to controls was observed in male rats at a dosage of 145 ppm.

Survival was not affected. The occurrence of rough hair and arched backs was seen only in the male rats receiving the highest dosage of 3155 ppm (5/5 males). No other compound-related abnormalities were observed. Results of the subchronic study in mice are reported in Table 5-4. Decreases in mean body weight gain were observed in mice. No other compound-related effects were seen. Chronic administration of 4,4'-methylenebis(N,N-dimethylaniline) in the diet of rats at 375 and 750 ppm for 59 weeks, followed by a 45-week observation period, resulted in decreased body weight gain in male rats after week 30 (high-dose males only). A dose-related trend in body weight depression was apparent in female rats after week 35. Nonneoplastic lesions observed in dosed, but not control, rats were associated with the thyroid gland (see Section 5.5.). Dosed male and female rats had increased incidences of follicular cysts, hyperplasia and C-cell hyperplasia. Chronic administration of the compound to mice in the diet at 1250 and 2500 for 78 weeks followed by a 13-week observation period resulted in decreased mean body weight gain in dosed male mice after week 30. A dose-related trend in decreased body weight of female mice was observed after week 30. Compound-related nonneoplastic lesions induced in dosed mice had increased incidences of thyroid papillary hyperplasia and adenomatous goiter.

Because results of the NCI (1979) bioassay indicated an increased incidence of compound-related neoplasms of the thyroid in dosed male and female rats, and an increased incidence of hepatocellular neoplasms in female mice, it is appropriate to derive a carcinogenic potency factor ($q_1^*$) for humans for 4,4'methylenebis(N,N-dimethylaniline). The tumor incidences and data used to calculate the $q_1^*$ for the compound are presented in Tables 8-1 to 8-6 and summarized in Table 8-7. The dietary concentrations were converted to dosages in mg/kg/day by assuming that rats and

TABLE 8-1

Cancer Data Sheet for
Derivation of $q_1^*$

Compound: 4,4'-methylenebis(N,N-dimethyl)aniline

Reference: NCI, 1979

Species, Strain, Sex: rat, F344, M

Body weight: 0.4 kg (measured)

Length of exposure (le) = 59 weeks

Length of experiment (Le) = 104 weeks

Lifespan of animal (L) = 104 weeks

Tumor site and type: thyroid, follicular cell carcinoma/adenoma

Route, vehicle: oral, diet

| Experimental Doses or Exposures (ppm) | Transformed Dose (mg/kg/day) | Incidence No. Responding/ No. Tested or Examined |
|---|---|---|
| 0 | 0 | 1/18 |
| 375 | 10.64 | 4/50 |
| 750 | 21.27 | 34/46 |

Note: Goodness of fit not adequate; therefore, high dose was dropped from the derivation of $q_1^*$.

Unadjusted $q_1^*$ from study = $1.2773594 \times 10^{-2}$ $(mg/kg/day)^{-1}$

Human $q_1^*$ = $7.1448392 \times 10^{-2}$ $(mg/kg/day)^{-1}$

TABLE 8-2

Cancer Data Sheet for
Derivation of $q_1^*$

Compound: 4,4'-methylenebis(N,N-dimethyl)aniline

Reference: NCI, 1979

Species, Strain, Sex: rat, F344, M

Body weight: 0.4 kg (measured)

Length of exposure (le) = 59 weeks

Length of experiment (Le) = 104 weeks

Lifespan of animal (L) = 104 weeks

Tumor site and type: thyroid, follicular cell carcinoma

Route, vehicle: oral, diet

| Experimental Doses or Exposures (ppm) | Transformed Dose (mg/kg/day) | Incidence No. Responding/ No. Tested or Examined |
|---|---|---|
| 0 | 0 | 1/18 |
| 375 | 10.64 | 4/50 |
| 750 | 21.27 | 21/46 |

Unadjusted $q_1^*$ from study = $1.0135779 \times 10^{-2}$ $(mg/kg/day)^{-1}$

Human $q_1^*$ = $5.6694004 \times 10^{-2}$ $(mg/kg/day)^{-1}$

TABLE 8-3

Cancer Data Sheet for
Derivation of $q_1^*$

Compound: 4,4'-methylenebis(N,N-dimethyl)aniline

Reference: NCI, 1979

Species, Strain, Sex: rat, F344, F

Body weight: 0.25 kg (measured)

Length of exposure (le) = 59 weeks

Length of experiment (Le) = 104 weeks

Lifespan of animal (L) = 104 weeks

Tumor site and type: thyroid, follicular cell carcinoma

Route, vehicle: oral, diet

| Experimental Doses or Exposures (ppm) | Transformed Dose (mg/kg/day) | Incidence No. Responding/ No. Tested or Examined |
|---|---|---|
| 0 | 0 | 0/20 |
| 375 | 10.64 | 3/46 |
| 750 | 21.27 | 23/45 |

Unadjusted $q_1^*$ from study = $9.4457249 \times 10^{-3}$ mg/kg/day)$^{-1}$

Human $q_1^*$ = $6.1795185 \times 10^{-2}$ (mg/kg/day)$^{-1}$

TABLE 8-4

Cancer Data Sheet for
Derivation of $q_1^*$

Compound: 4,4'-methylenebis(N,N-dimethyl)aniline

Reference: NCI, 1979

Species, Strain, Sex: rat, F344, F

Body weight: 0.25 kg (measured)

Length of exposure (le) = 59 weeks

Length of experiment (Le) = 104 weeks

Lifespan of animal (L) = 104 weeks

Tumor site and type: thyroid, follicular cell carcinoma/adenoma

Route, vehicle: oral, diet

| Experimental Doses or Exposures (ppm) | Transformed Dose (mg/kg/day) | Incidence No. Responding/ No. Tested or Examined |
|---|---|---|
| 0 | 0 | 0/20 |
| 375 | 10.64 | 4/46 |
| 750 | 21.27 | 36/45 |

Note: Goodness of fit not adequate; therefore, high dose was dropped from the derivation of $q_1^*$.

Unadjusted $q_1^*$ from study = $1.7634258 \times 10^{-2}$ $(mg/kg/day)^{-1}$

Human $q_1^*$ = $1.1536565 \times 10^{-1}$ $(mg/kg/day)^{-1}$

TABLE B-5

Cancer Data Sheet for
Derivation of $q_1^*$

Compound: 4,4'-methylenebis(N,N-dimethyl)aniline

Reference: NCI, 1979

Species, Strain, Sex: mice, B6C3F1, M

Body weight: 0.035 kg (measured)

Length of exposure (le) = 78 weeks

Length of experiment (Le) = 91 weeks

Lifespan of animal (L) = 104 weeks

Tumor site and type: liver, hepatocellular carcinoma/adenoma

Route, vehicle: oral, diet

| Experimental Doses or Exposures (ppm) | Transformed Dose (mg/kg/day) | Incidence No. Responding/ No. Tested or Examined |
|---|---|---|
| 0 | 0 | 5/20 |
| 1250 | 139.29 | 12/50 |
| 2500 | 278.57 | 22/48 |

Unadjusted $q_1^*$ from study = $1.6959875 \times 10^{-3}$ $(mg/kg/day)^{-1}$

Human $q_1^*$ = $3.1896411 \times 10^{-3}$ $(mg/kg/day)^{-1}$

TABLE 8-6

Cancer Data Sheet for
Derivation of $q_1^*$

Compound: 4,4'-methylenebis(N,N-dimethyl)aniline

Reference: NCI, 1979

Species, Strain, Sex: mice, B6C3F1, F

Body weight: 0.03 kg (measured)

Length of exposure (le) = 78 weeks

Length of experiment (Le) = 91 weeks

Lifespan of animal (L) = 104 weeks

Tumor site and type: liver, hepatocellular carcinoma/adenoma

Route, vehicle: oral, diet

| Experimental Doses or Exposures (ppm) | Transformed Dose (mg/kg/day) | Incidence No. Responding/ No. Tested or Examined |
|---|---|---|
| 0 | 0 | 1/19 |
| 1250 | 139.29 | 19/49 |
| 2500 | 278.57 | 23/48 |

Unadjusted $q_1^*$ from study = $3.3001558 \times 10^{-3}$ $(mg/kg/day)^{-1}$

Human $q_1^*$ = $6.5338508 \times 10^{-2}$ $(mg/kg/day)^{-1}$

TABLE 8-7

Summary Data Sheet for Derivation of $q_1^*$ for
4,4'-Methylenebis(N,N-dimethylaniline)

| Tumor Site/Type | Species | $q_1^*$ M $(mg/kg/day)^{-1}$ | $q_1^*$ F $(mg/kg/day)^{-1}$ |
|---|---|---|---|
| Thyroid: | | | |
| Follicular-cell carcinoma/adenoma | F344 rat | $7.1448392 \times 10^{-2}$ | $1.1536565 \times 10^{-1}$ |
| Follicular-cell carcinoma | F344 rat | $5.6694004 \times 10^{-2}$ | $6.179518 \times 10^{-2}$ |
| Liver: | | | |
| Hepatocellular carcinoma/adenoma | B6C3F1 mice | $3.1896411 \times 10^{-2}$ | $6.5338508 \times 10^{-2}$ |

mice consume a daily amount of food equal to 5 and 13%, respectively, of the body weight and by multiplying by le/Le. The unadjusted values for $q_1^*$ were calculated using the linearized multistage model developed by Kenneth Crump and adopted by the U.S. EPA (Federal Register, 1980). The conversion factor used in the calculation of the $q_1^*$ values for humans (assuming 70 kg bw) from the unadjusted values was the cube root of the ratio of the human body to the animal body weight. Body weights used for rats and mice were obtained from the NCI (1979) data as follows: 0.4 kg, male rats; 0.25 kg, female rats; 0.035 kg, male mice; and 0.03 kg, female mice. Since the length of the experiment in mice was less than the lifespan of mice, the unadjusted values were further corrected by $(L/Le)^3$.

As seen in Tables 8-1 and 8-4, the dose response data did not adquately fit the model; therefore, the highest dose was dropped, and the $q_1^*$ recalculated based on the tumor incidence data at the low- and mid-doses. Since the $q_1^*$ of $1.1536565 \times 10^{-1}$ $(mg/kg/day)^{-1}$ resulting from the combined tumor incidence of thyroid-follicular cell carcinoma/adenoma following ingestion of the compound by female rats is higher than that generated from other tumor data (see Table 8-7), it is recommended for estimating the increased lifetime risk of human exposure to 4,4'-methylenebis(N,N-dimethylaniline).

## 9. REPORTABLE QUANTITIES

### 9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

One chronic study in rats and mice was available for consideration in deriving CSs and RQs for 4,4'-methylenebis(N,N-dimethylaniline) (NCI, 1979). This study is summarized in Table 9-1, and the data used to calculate CSs and RQs are summarized in Table 9-2.

Human MEDs were calculated from the animal dosages by multiplying by the cube root of the ratio of the animal body weight to the weight of a human (70 kg) and by 70 kg to express the MED in mg/day. The animal body weights used were those of female rats and mice [0.25 and 0.03 kg, respectively, as estimated from the growth curves in NCI (1979)] since these body weights were lower than those of the male animals. The $RV_d$s associated with MEDs ranged from 1.2-2.4. The effects of hyperplasia and decreased body weight gains warrant $RV_e$s of 3 and 4, respectively. The highest CS of 8 ($RV_d$ x $R_e$) was obtained for decreased body weight gain observed in high-dose rats and corresponds to an RQ of 1000 (Table 9-3).

### 9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

Results from a 2-year feeding study indicated that 4,4'-methylenebis-(N,N-dimethylaniline) produced an increased incidence of thyroid follicular-cell adenoma/carcinoma in both male and female F344 rats and hepatocellular neoplasms in female B6C3F1 mice (see Section 5.1.). The results of this study are presented in Table 9-4. The compound was tested in both sexes of more than one species for a significant part of the animals' lifespan and a sufficient number of animals/group were evaluated. Therefore, the data are sufficient to suggest that the compound is carcinogenic to animals, may be a potential carcinogen for humans, and should be placed in IARC Group 2B.

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TABLE 9-1

Oral Toxicity Summary for 4,4-Methylenebis(N,N-dimethylaniline)

| Species/ Strain | Sex | Number at Start | Vehicle | Purity | Dosage/Exposure | Dose* (mg/kg/day) | Response | Reference |
|---|---|---|---|---|---|---|---|---|
| rat/F344 | M,F | 50, 50 | diet | technical grade | 375 ppm for 59 weeks, then 0 ppm for 45 weeks | 10.64 | increased incidence of thyroid gland follicular cysts, follicular hyperplasia and C-cell hyperplasia | NCI, 1979 |
| rat/F344 | M,F | 50, 50 | diet | technical grade | 750 ppm for 59 weeks, then 0 ppm for 45 weeks | 21.27 | decreased body weight gain | NCI, 1979 |
| mice/ B6C3F1 | M,F | 50, 50 | diet | technical grade | 1250 ppm for 78 weeks, then 0 ppm for 13 weeks | 139.29 | decreased mean body weight gain, thyroid papillary hyperplasia, adenomatous goiter | NCI, 1979 |

*The doses were calculated assuming that rats and mice consume a daily amount of food equal to 5 and 13%, respectively, of the body weight. The resultant dose was multiplied by the number of weeks of treatment and divided by the number of weeks of the experiment.



08/20/85

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TABLE 9-2

Composite Scores for Toxicity of 4,4'-Methylenebis(N,N-dimethylaniline) Administered to Rats and Mice in the Diet

| Species | Dose/Exposure | Chronic Human MED (mg/day) | $RV_d$ | Effects | $RV_e$ | CS | RQ | Reference |
|---|---|---|---|---|---|---|---|---|
| Rat | 10.64 mg/kg/day for 2 years | 113.8 | 2.4 | thyroid gland follicular cysts, follicular hyperplasia and C-cell hyperplasia | 3 | 7.2 | 1000 | NCI, 1979 |
| Rat | 21.27 mg/kg/day for 2 years | 227.6 | 2.0 | decreased body weight gain | 4 | 8.0 | 1600 | NCI, 1979 |
| Mouse | 139.29 mg/kg/day for 91 weeks | 735.1 | 1.2 | decreased body weight gain, thyroid papillary hyperplasia, adenomatous goiter | 4 | 4.8 | 5000 | NCI, 1979 |



08/20/85

TABLE 9-3

4,4'-Methylenebis(N,N-dimethylaniline)

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

| | |
|---|---|
| Route: | oral/diet |
| Dose*: | 227.6 mg/day |
| Effect: | decreased body weight gain |
| Reference: | NCI, 1979 |
| $RV_d$: | 2.0 |
| $RV_e$: | 4 |
| Composite Score: | 8 |
| RQ: | 1000 |

*Equivalent human dose

TABLE 9-4

Oral Exposure to 4,4-Methylenebis(N,N-dimethylaniline)[a]

| Species/ Strain | Sex | Dose[b] (ppm) | Duration of Treatment (weeks) | Duration of Study (weeks) | Purity of Compound | Vehicle or Physical State | Target Organ | Tumor Type | Tumor Incidence (P value) |
|---|---|---|---|---|---|---|---|---|---|
| rats/F344 | M | 0<br>375<br>750 | 59 | 104 | technical grade | diet | thyroid | follicular-cell carcinoma | 1/18 (p<0.001))[b]<br>4/50<br>21/46 (p=0.002)[c] |
| | | 0<br>375<br>750 | | | | | | follicular-cell adenoma | 0/18<br>0/50<br>13/46 |
| | | 0<br>375<br>750 | | | | | | follicular-cell carcinoma/adenoma | 1/18 (p<0.001)[b]<br>4/50<br>34/46 (p<0.001)[c] |
| | | 0<br>375<br>750 | | | | | | C-cell carcinoma/adenoma | 2/18<br>2/50<br>4/46 |
| rats/F344 | F | 0<br>375<br>750 | 59 | 104 | technical grade | diet | thyroid | follicular-cell carcinoma | 0/20 (p<0.001)[b]<br>3/46<br>23/45 (p<0.001)[c] |
| | | 0<br>375<br>750 | | | | | | follicular-cell adenoma | 0/20<br>1/46<br>13/45 |
| | | 0<br>375<br>750 | | | | | | follicular-cell carcinoma/adenoma | 0/20 (p<0.001)[b]<br>4/46<br>36/45 (p<0.001)[c] |
| | | 0<br>375<br>750 | | | | | | C-cell carcinoma/adenoma | 2/20<br>2/46<br>1/45 |
| mice/ B6C3F1 | M | 0<br>1250<br>2500 | 78 | 91 | technical grade | diet | liver | hepatocellular carcinoma | 3/20<br>9/50<br>6/48 |
| | | 0<br>1250<br>2500 | | | | | | hepatocellular carcinoma/or adenoma | 5/20 (p=0.025)[b]<br>12/50<br>22/48 |

TABLE 9-4 (cont.)

| Species/ Strain | Sex | Dose[b] (ppm) | Duration of Treatment (weeks) | Duration of Study (weeks) | Purity of Compound | Vehicle or Physical State | Target Organ | Tumor Type | Tumor Incidence (P value) |
|---|---|---|---|---|---|---|---|---|---|
| mice/ B6C3F1 | F | 0<br>1250<br>2500 | 78 | 91 | technical grade | diet | liver | hepatocellular carcinoma | 0/19<br>1/49<br>1/48 |
| | | 0<br>1250<br>2500 | | | | | | hepatocellular carcinoma/or adenoma | 1/19 (p=0.002[b])<br>19/49 (p=0.005[c])<br>23/48 (p=0.001[c]) |

QUALITY OF EVIDENCE

Stengths of Study: Several dose levels studied in both sexes of more than one species. A sufficient number of animals per species and sex was evaluated (50). Control groups consisted of 20 animals/sex/species. Comprehensive histologic examination was performed. Appropriate statistical methods were employed.

Overall Adequacy: Adequate

[a]NCI, 1979

[b]Cochran-Armitage test for linear trend, probability level for significance p<0.05

[c]One tailed Fisher Exact test for comparison of tumor indicence between treated group and control group, probability level for significance p<0.05

This corresponds to group B2, probable human carcinogens using the CAG classification system (U.S. EPA, 1984). The category indicates sufficient evidence in animals with inadequate evidence from human studies.

The dose-response data indicating an increased incidence of thyroid follicular-cell adenoma/carcinoma in female rats were used to calculate an unadjusted $1/ED_{10}$ for 4,4'-methylenebis(N,N-dimethylaniline) (Table 9-5), using the linearized multistage model developed by Crump and adopted by the U.S. EPA (Federal Register, 1980). Because the goodness of fit hypothesis for the rat data was rejected, the highest dose level was dropped and the unadjusted $ED_{10}$ was recalculated. The dose in mg/kg/day was calculated from the dietary levels by assuming that a rat consumes a daily amount of food equal to 5% of its body weight. The resultant dose was further corrected by multiplying by the duration of treatment and dividing by the duration of the study. The unadjusted $1/ED_{10}$ was converted to the F factor by multiplying by the cube root of the ratio of the human body weight (70 kg) to the animal weight [0.25 kg, as estimated from the growth curve as presented in NCI (1979)]. The data for female rats resulted in the F factor, 5.57 $mg/kg/day^{-1}$.

Because the F factor falls between 1 and 10, 4,4'-methylenebis(N,N-dimethylaniline) is placed in Potency Group 3. A chemical in Potency Group 3 and IARC Group 2B has a medium hazard ranking according to the scheme for reportable quantities under CERCLA.

TABLE 9-5

Derivation of Potency Factor (F)
Agent: 4,4'-Methylenebis(N,N-dimethylaniline)

| | | | |
|---|---|---|---|
| Reference: | NCI, 1979 | | |
| Exposure route: | oral | | |
| Species: | rat | | |
| Strain: | F344 | | |
| Sex: | female | | |
| Vehicle or physical state: | diet | | |
| Body weight*: | 0.25 kg females | | |
| Duration of treatment: | 59 weeks | | |
| Duration of study: | 104 weeks | | |
| Lifespan of animal: | 104 weeks | | |
| Target organ: | thyroid | | |
| Tumor type: | follicular cell carcinoma/adenoma | | |
| Experimental doses/ exposure (ppm): | 0 | 375 | 750 |
| Transformed doses (mg/kg/day): | 0 | 10.64 | 21.27 |
| Tumor incidence: | 0/20 | 4/46 | 36/45 |
| Unadjusted $1/ED_{10}$: | $8.51 \times 10^{-1}$ | | |
| $1/ED_{10}$ (F factor): | 5.57 $(mg/kg/day)^{-1}$ | | |

*Reported

## 10. REFERENCES


Bannister, D. and J. Elliot. 1978. Triphenylmethane and related dyes. In: Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed., Vol. 23, M. Grayson and D. Eckroth, Ed. John Wiley and Sons, Inc. NY. p. 399-412.

Dieke, S.H., G.S. Allen and C.P. Richter. 1947. The acute toxicity of thioureas and related compounds to wild and domestic Norway rats. J. Pharmacol. Exp. Therapeut. 90: 260-270. (Cited in U.S. EPA, 1981)

Dunkel, V.C. and V.F. Simmon. 1980. Mutagenic activity of chemicals previously tested for carcinogenicity in the National Cancer Institute bioassay program. IARC Sci. Publ. 27: 283-302.

E.I. Du Pont de Nemours and Co. 1969. Product bulletin for ortholeum 304.A-15803-1. E.I. Du Pont de Nemours and Co., Willmington, DE. (Cited in U.S. EPA, 1981)

E.I. Du Pont de Nemours and Co. 1981. Personal communication; unidentified spokesman. E.I. Du Pont de Nemours and Co., Willmington, DE. (Cited in U.S. EPA, 1981)

Federal Register. 1980. Guidelines and methodology used in the preparation of health effects assessment chapters of the Consent Decree Water Criteria Documents. 45 FR 79347-79357.

Hawley, G.G. 1981. The Condensed Chemical Dictionary, 10th ed. Van Nostrand Reinhold Company, New York. p. 1009.

IARC (International Agency for Research on Cancer). 1982. 4,4'-Methylene-bis(N,N-dimethyl)benzenamine. In: Some aromatic amines, anthraquinones and nitroso compounds and inorganic fluorides used in drinking water and dental preparations. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyon, France. Vol. 27, p. 119.

Legator, M.S., E. Bueding, R. Batzinger, et al. 1982. An evaluation of the host-mediated assay and body fluid analysis. A Report of the U.S. Environmental Protection Agency Gene-Tox Program. Mutat. Res. 98(3): 319-374.

Leifer, Z, J. Hyman and H.S. Rosenkranz. 1981. Determination of genotoxic activity using DNA polymerase-deficient and -proficient E. coli (complete title not available). Short-Term Tests Chem. Carcinogen. 127-139. (CA 95-36436)

Maronpot, R.R., H.P. Witschi, L.H. Smith and J.L. McCoy. 1983. Recent experience with the strain A mouse pulmonary tumor bioassay model. Environ. Sci. Res. 27: 341-349.

McCarthy, D.J., R.F. Struck, T.W. Shih, W.J. Suling, D.L. Hill and S.E. Enke. 1982. Disposition and metabolism of the carcinogen reduced Michler's ketone in rats. Cancer Res. 42(9): 3475-3479.

McCarthy, D.J., W.J. Suling and D.L. Hill. 1983. A comparison of the mutagenicity and macromolecular binding of the carcinogens Michler's ketone and reduced Michler's ketone. Mutat. Res. 119(1): 7-14.

Mitchell, A.D., C.J. Rudd, B.C. Myhr, W.J. Caspary, S. Poulton and Y.J. Lee. 1982. L5178Y TK+/- mouse lymphoma cell mutagenesis assays of 40 coded compounds: Results from two laboratories and comparisons with results from other in vitro and in vivo bioassays. Environ. Mutagen. 4: 394-395.

Murthy, A.S.K. 1980. Morphology of the neoplasms of the thyroid gland in Fischer 344 rats treated with 4,4'-methylene-bis(N,N-dimethyl)benzenamine. Toxicol. Lett. 6(6): 391-397.

NCI (National Cancer Institute). 1979. Bioassay of 4,4'-methylene(N,N-dimethyl)benzenamine for possible carcinogenicity. CAS No. 101-61-1. NCI Tech. Rep. 186.

Nelson, C.R. and R.A. Hites. 1980. Aromatic amines in and near the Buffalo River. Environ. Sci. Technol. 14: 1147-1149.

NIOSH (National Institute for Occupational Safety and Health). 1979. Registry of toxic effects of chemical substances. NIOSH, Cincinnati, OH.

NTP, 1983. Short-term in vitro mammalian cell assay results. Tech. Bull. 9: 7.

NIOSH (National Institute for Occupational Safety and Health). 1981. Trade name ingredient data base, Washington, DC. (Cited in U.S. EPA, 1981)

Pienta, R.J. and J.C. Kawalek. 1981. Transformation of hamster embryo cells by aromatic amines. Natl. Cancer Inst. Monogr. 58: 243-251.

Rosenkranz, H.S. and L.A. Poirier. 1979. Evaluation of the mutagenicity and DNA-modifying activity of carcinogens and noncarcinogens in microbial systems. J. Natl. Cancer Inst. 62(4): 873-892.

Sabljic, A. 1984. Prediction of the nature and strength of soil sorption of organic pollutants by molecular topology. J. Agric. Food Chem. 32: 243-246.

Scribner, J.D., G. Koponen, S.R. Fisk and B. Woodworth. 1980. Binding of the dye intermediates Michler's ketone and methane base to rat liver nucleic acids and lack of mutagenicity in Salmonella typhimurium. Cancer Lett. 9(2): 117-121.

Simmon, V.F. 1979a. In vitro mutagenicity assays of chemical carcinogens and related compounds with Salmonella typhimurium. J. Natl. Cancer Inst. 62(4): 893-899.

Simmon, V.F. 1979b. In vitro assays for recombinogenic activity of chemical carcinogens and related compounds with Saccharomyces cerevisiae D3. J. Natl. Cancer Inst. 62(4): 901-904.

Simmon, V.F., H.S. Rosenkranz, E. Zeiger and L.A. Poirier. 1979. Mutagenic activity of chemical carcinogens and related compounds in the intraperitoneal host-mediated assay. J. Natl. Cancer Inst. 62(4): 911-918.

SRI (Stanford Research Institute) International. 1984. Directory of Chemical Producers. SRI International, Menlo Park, CA.

The Society of Dyers and Colourists. 1971. Colour Index, 3rd ed., Vol. 4. Lund Humphries Printers, London, England. p. 4703. (Cited in IARC, 1982)

U.S. EPA. 1981. Chemical Hazard Information Profile. Draft report, 4,4'-methylenebis(N,N-dimethyl)benzenamine. Prepared by SRI International. U.S. EPA, Washington, DC.

U.S. EPA. 1984. Proposed Guidelines for Carcinogen Risk Assessment. Fed. Reg. 49(227): 46294-46299.

U.S. EPA. 1985. TSCAPP (Toxic Substances Control Act Plant and Production) Search System. Search through CIS.

USITC (United States International Trade Commission). 1976. Synthetic Organic Chemicals, United States Production and Sales. USITC Publ. 776. p. 22.

USITC (United States International Trade Commission). 1978. Synthetic Organic Chemicals, United States Production and Sales. USITC Publ. 920. p. 48.

USITC (United States International Trade Commission). 1980. Synthetic Organic Chemicals, United States Production and Sales. USITC Publ. 1099. p. 50, 77.

USITC (United States International Trade Commission). 1984. Synthetic Organic Chemicals, United States Production and Sales. USITC Publ. 1548. p. 28.

Waalkens, D.H., H.F.P. Joosten, T.D. Yih and A. Hoekstra. 1981. Mutagenicity studies with o-toluidine and 4,4'-tetramethyldiaminodiphenylmethane. Mutat. Res. 89(3): 197-202.

Weast, R.C., Ed. 1972. Handbook of Chemistry and Physics, 54th ed. Chemical Rubber Company, Cleveland, OH. p. C-366.

Weisburger, E.K. 1983. Species differences in response to aromatic amines. Basic Life Sci. 24: 23-47.

Weisburger, E.K., A.S. Krishna Murthy, H.S. Lilja, J.C. Lamb IV. 1984. Neoplastic response of F344 rats and B6C3F1 mice to the polymer and dyestuff intermediates 4,4'-methylenebis(,N-dimethyl)benzenamine, 4,4'-oxydianiline, and 4,4'-methylenedianiline. J. Natl. Cancer Inst. 72(6): 1457-1463.

Williams, G.M., M.F. Laspia and V.C. Dunkel. 1982. Reliability of the hepatocyte primary culture/DNA repair test in testing of coded carcinogens and noncarcinogens. Mutat. Res. 97(5): 359-370.

Windholz, M., Ed. 1976. The Merck Index, 9th ed. Merck and Company, Rahway, NJ. p. 1189.

## APPENDIX A

## LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CA SEARCH (Files 308, 309, 310, 311, 320
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in February, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:


ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1983. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1983-1984. Cincinnati, OH. 94 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. p. 3817-5112.

Grayson, M. and D. Eckroth, Eds. 1978-83. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Vol.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technology Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

NTP (National Toxicology Program). 1984. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.

Sax, I.N. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nos Reinhold Co., NY.

SRI (Stanford Research Institute). 1984. Directory of Chemical Producers. Stanford, CA.

U.S. EPA. 1982. Chemical Activities Status Report, 3rd ed. (EPACASR). Offices of Pesticides and Toxic Substances, Washington, DC. EPA 560/TIIS-82-002b.

U.S. EPA. 1983. Status Report on Rebuttable presumption Against Registration (RPAR) or Special Review Process. Registration Standards and the Data Call in Programs. Office of Pesticide Programs, Washington, DC.

U.S. EPA. 1984. CSB Existing Chemical Assessment Tracking System. Name and CAS Number Ordered Indexes. Office of Toxic Stustances, Washington, DC.

USITC (United States International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982. USITC Publ. 1422. Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:


Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book, Vol. 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish Wildl. Ser. Resource Publ. 137. Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California. State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effect of Pesticides on Non-Target Species. PB 269605. Prepared for the U.S. EPA, Washington, DC.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs. U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.